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Normalization of Plasma Factor X Levels in Amyloidosis After Plasma Exchange

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Some patients with systemic light chain amyloidosis develop bleeding complications that can be caused by vascular infiltration with amyloid or by alterations of the coagulation or fibrinolytic systems. Factor X deficiency is the most common cause of bleeding manifestations, although deficiencies of other clotting factors, a disruption in the conversion of fibrinogen to fibrin, and circulating heparin-like anticoagulants have also been reported. Deficiency of factor X is a well-recognized cause of bleeding manifestations in patients with light chain amyloidosis. This acquired disorder appears to be secondary to adsorption of factor X to the amyloid fibrils. Previous studies have shown that infusion of plasma into patients with acquired factor X deficiency and amyloidosis induces a transitory improvement of the coagulation tests. However, there is a rapid return to pretransfusion levels. In this manuscript we report the clinical application of plasma exchange in the management of a patient with systemic light chain amyloidosis with acquired factor X deficiency. Am. J. Hematol. 54:68–71, 1997

Key words: amyloid; plasmapheresis; factor X deficiency

INTRODUCTION

Some patients with systemic light chain amyloidosis develop bleeding complications that can be caused by vascular infiltration with amyloid or by alterations of the coagulation or fibrinolytic systems. Factor X deficiency is the most common cause of bleeding manifestations, although deficiencies of other clotting factors, a disruption in the conversion of fibrinogen to fibrin, and circulating heparin-like anticoagulants have also been reported [1,5].

Deficiency of factor X is a well-recognized cause of bleeding manifestations in patients with light chain amyloidosis. This acquired disorder appears to be secondary to adsorption of factor X to the amyloid fibrils [3]. Previous studies have shown that infusion of plasma into patients with acquired factor X deficiency and amyloidosis induces a transitory improvement of the coagulation tests. However, there is a rapid return to pretransfusion levels [8]. In this manuscript we report the clinical application of plasma exchange in the management of a patient with systemic light chain amyloidosis with acquired factor X deficiency.

CASE REPORT

A 55-year-old white woman presented in October 1991 with right upper quadrant pain and massive hepatosplenomegaly. Biopsy of the liver demonstrated apple-green birefringence on congo red staining diagnostic of amyloidosis. Electron microscopy of the liver showed severe amyloid deposition. Serum protein immuno-electrophoresis was remarkable for a monoclonal IgG kappa gammopathy with depression of total serum IgA and IgM levels. Free kappa light chain proteinuria was present. Initial laboratory studies in our institution March 2, 1992 gave a prothrombin time (PT) of 15.6 sec (n = 11.6–13.8 sec) and an activated partial thromboplastin time (aPTT) of 41.8 sec (n = 23.6–36.8 sec). Mixing the patient's plasma 1:1 with normal pooled plasma corrected the PT to 12.7

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TABLE I. Coagulation Studies*

Test	9-9-94[a]	9-9-94[b]	9-20-94[c]	9/20/94[d]	Normal
Time	0730	1325	0730	1445	
PT/mix	16.7/12.9	16.3	18.0/nd	14.9	11.6–13.8
aPTT/mix	33.2/nd	32.6	36.3/nd	33.5	23.6–36.8
TT/mix	25.7/22.7	nd	nd	nd	<24.0
Fibrinogen	nd	nd	nd	nd	166–394
Factor II	0.54	nd	nd	nd	0.75–1.50
Factor V	0.60	nd	nd	nd	0.47–1.53
Factor VII	0.50	nd	nd	nd	0.57–1.43
Factor X	0.27	nd	0.25	0.43	0.58–1.42

*PT = prothrombin time; aPTT = activated partial thromboplastin time; TT = thrombin time (all times in seconds). Factor levels in U/milliliter. Fibrinogen units are μg/dl; nd = no data.
[a]Studies on patient immediately prior to infusion of 7 U of fresh frozen plasma.
[b]Studies on patient post infusion of plasma.
[c]Studies on patient immediately prior to plasma exchange transfusion.
[d]Studies on patient immediately post plasma exchange transfusion.

sec and the aPTT to 34.6 sec. Bone marrow aspirate and biopsy were suggestive of amyloid infiltration, but no other abnormalities were noted.

In May of 1994, she developed hemorrhoidal bleeding, which was more severe during exercise and limited her physical activities. Conservative measures were unsuccessful in controlling bleeding and the patient became progressively more anemic. Because of this, in September 1994 the patient was scheduled for elective hemorrhoidectomy on the surgical service. On September 9, 1994 her factor X level was 0.27 U/ml, the prothrombin time was 16.7 sec, and her platelet count was 99,000/dl. Mixing the patient's plasma 1:1 with normal pooled plasma again demonstrated correction of the PT to 12.9 sec. The other factor levels were normal (Table I). In an attempt to correct the coagulation disorder 3 U of fresh frozen plasma (FFP) were adminsitered and a repeat prothrombin time was found to be 16.1 sec. Four more units of FFP were administered and the PT remained unchanged at 16.3 sec and the surgery was postponed.

Ten days later she was readmitted for plasma exchange transfusion. Prior to aphersis the PT was 18 sec and the factor X level was 0.25 U/ml. A 2 liter total isovolume plasma exchange was performed and the PT decreased to 14.9 sec and the factor X level rose to 0.43 U/ml. Internal hemorrhoidectomy was performed without immediate blood loss. Postoperatively she received 3 U FFP, but subsequently developed severe rectal bleeding. Epsilon-amino-caproic acid was started intravenously at a dose of 2 g per hour after a loading bolus of 4 g. Repeat PT was 20.1 sec and the factor X level was 0.29 U/ml. Plasma exchange transfusion was again performed with isovolume replacement with FFP and the PT decreased to 16.5 sec. There was no further rectal bleeding. The following day the PT was 15.2 sec and the factor X level was 0.38 U/ml. A third plasma exchange transfusion was performed. Follow-up PT was 14.3 sec. The following day the PT was 14.3 U/ml and the factor X was 0.48 U/ml and she was given an additional 3 U FFP. Twenty-four hours later the PT was 13.5 sec. She was discharged home the following day.

Her PT and factor X levels 3 days, 10 days, and 6 weeks after discharge were 13.7 sec, 0.48 U/ml; 14.5 sec, 0.36 U/ml; and 18.3 sec, 0.25 U/ml, respectively. She has had no further rectal bleeding. Pathologic examination of the excised hemorrhoidal tissue did not demonstrate the presence of amyloid deposits.

METHODS

Blood was collected from the patient in vacutainer tubes containing 3.8% sodium citrate and was immediately centrifuged at 3,000 rpm for 15 min at 4°C and the plasma separated for analysis.

The prothrombin time (PT) was measured using the one stage prothrombin time determination method. Plasma was added to a pre-warmed rabbit brain thromboplastin-calcium mixture (Ortho Brain Thromboplastin, Ortho Diagnostic Systems, Raritan, NJ) and the time required for clot formation was determined [7]. The International Normalized Ratio (INR) was calculated as follows: $INR = (\text{Patient PT/mean PT pooled plasma})^{ISI}$, where the ISI is the International Standardized Index for the thromboplastin used.

The activated thromboplastin time (aPTT) was measured by the addition of thrombosil (Ortho Thrombosil, Ortho Diagnostic Systems) to patient plasma and incubated at 37°C for 5 min after which 0.02 M calcium chloride was added [7].

Mixing studies were performed by mixing patient plasma with normal pooled plasma. Mixing studies were routinely incubated at 37°C prior to analysis in the standard PT and aPTT assays [7].

Coagulation factor assays were performed by one stage

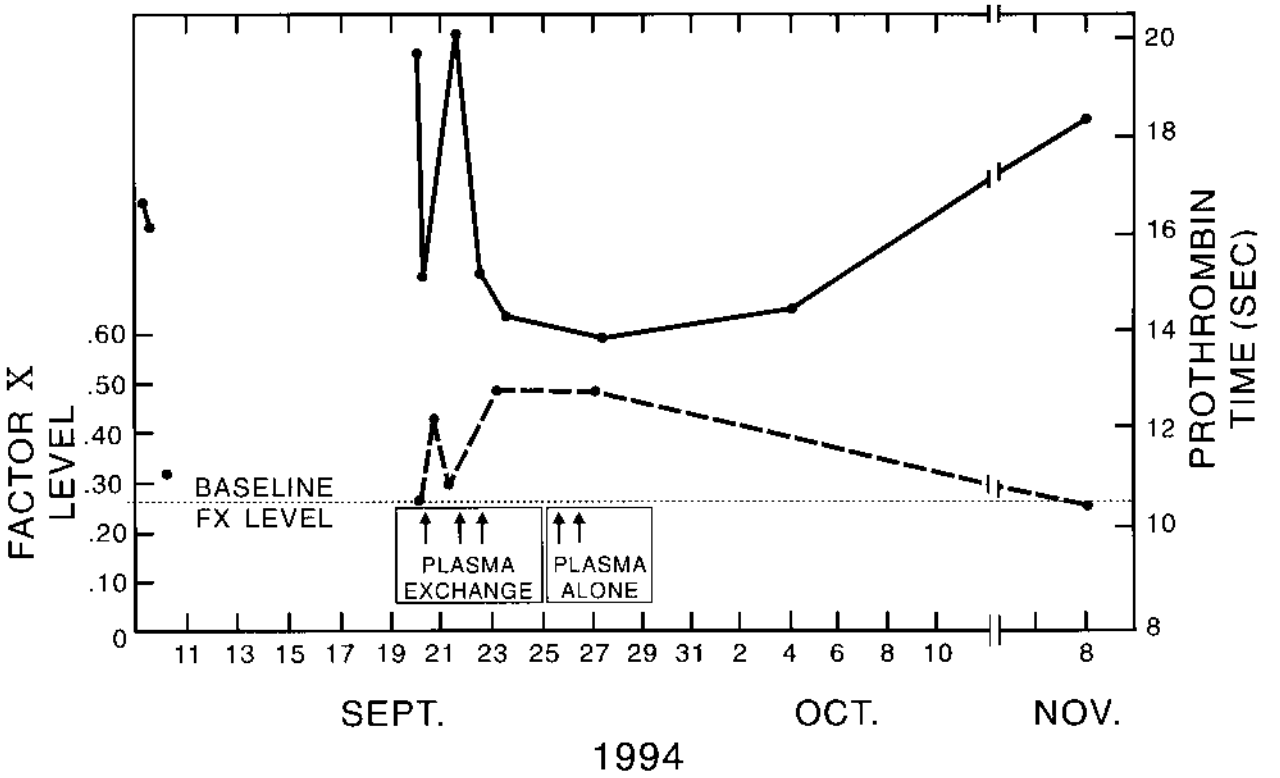

Fig. 1. Factor X levels and prothrombin times after plasma exchange transfusion and plasma infusion. (• – – – •) Factor X level; (•——•) prothrombin time.

sion should be undertaken to test responsiveness in a broad range of patients with amyloidosis.

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